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10/748,475	12/30/2003	Masad J. Damha	MGU-0025	7556

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,475	DAMHA ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10/21/2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 07/22/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 7/11/2005, claims 1 and 3-8 are pending in the application. Applicant has canceled claims 9-10.

Claim Rejections - 35 USC § 103

For purposes of prior art, the invention of the instant application is being interpreted to comprise a composition of Formula I, as shown in claim 1, wherein Y1 or Y2 can each be from 0 to 8 nucleotides in length and wherein at least one of Y1 or Y2 is from 4 to 8 nucleotides and further at least one of Y1 or Y2 comprises the sequence having SEQ ID NO. 1.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hannoush et al. (Document AE on Form PTO-1449 filed 10/04/2004) in view of Denisov et al. (Nucleic Acids Research, 2001).

Claim 1 is drawn to a composition comprising two complementary regions linked by 2', 5' ribonucleotides at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 wherein the complementary regions are between 2 and 24 nucleotides in length and comprise an arabinonucleic acid, 2'-fluoro-arabinonucleic acid, locked nucleic acid, peptide nucleic acid or a combination thereof and the complementary region is comprised of deoxyribonucleic acid or ribonucleic acid. Claims 3-5 recite the complementary regions are comprised of 3-, 5'-linked ribonucleic acid, deoxyribonucleic acid or a combination of both. Claims 6-7 recites the complementary region comprises a 3-, 5'-linked ribonucleic acid that are 4 to 10 nucleotides in length, the by 2', 5' linked ribonucleotides are a 3', 5'-linked tetranucleotide (SEQ ID NO:1).

Hannoush et al. teach a duplex oligonucleotide comprising an arabinonucleic acid and an ribonucleic acid, 4 nucleotides in length, wherein the duplex comprise 3', 5'-linked or 2', 5'-linked RNA wherein the duplex strands are linked by a tetranucleotide loop comprising SEQ ID NO. 1 (see Figure 1 and materials page 12369). Hannoush et al. does not teach a hairpin duplex comprising an arabinonucleic acid.

Denisov et al. teach a hairpin duplex comprising an arabinonucleic acid and the duplex can have increased flexibility that elicits RNAse H activity (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an arabinonucleic acid, as taught by Denisov et al. into the hairpin duplex taught by Hannoush et al.

One would have been motivated to incorporate an arabinonucleic acid into the oligonucleotide hairpin duplex taught by Hannoush et al because Denisov et al. teach a hairpin duplex comprising an arabinonucleic acid increases the flexibility and binding affinity to the target and further can elicit RNase H activity. Further, one would have been motivated to incorporate an arabinonucleic acid into the hairpin duplex because Denisov et al. teach that an hairpin duplex comprising an arabinonucleic acid elicits greater RNAse H activity because it adopt an east DNA-like conformation and displays greater flexibility to increase the binding affinity toward the target RNA (see page 4291). Additionally, one would have been motivated to incorporate an arabinonucleic acid into the hairpin duplex because Denisov et al. teach a hairpin duplex comprising an arabinonucleic acid is an important factor for RNase H recognition and cleavage of duplexes. Denisov et al. teach that all of the above factors are important for efficient therapeutic oligonucleotides.

Finally, one would have a reasonable expectation of success because Hannoush et al. teach that an oligonucleotide duplex comprising a tetranucleotide loop, having the sequence identical to SEQ ID NO. 1, increased the duplex thermostability and because Denisov et al. teach increased flexibility and target specificity when a duplex comprises an arabinonucleic acid.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 and 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wasner et al. (Document AM on Form PTO-1449 filed 10/04/2004) in view of Hannoush et al. (Document AE on Form PTO-1449 filed 10/04/2004) and in further view of Denisov et al. (Nucleic Acids Research, 2001).

Claim 1 is drawn to a composition comprising an inhibitory agent comprising two complementary regions linked by 2', 5' ribonucleotides at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 wherein the complementary regions are between 2 and 24 nucleotides in length and comprise an arabinonucleic acid, 2'-fluoro-arabinonucleic acid, locked nucleic acid, peptide nucleic acid or a combination thereof and the complementary region is comprised of deoxyribonucleic acid or ribonucleic acid. Claims 3-5 recite the complementary regions are comprised of 3-, 5'-linked ribonucleic acid, deoxyribonucleic acid or a combination of both. Claims 6-7 recites the complementary region comprises a 3-, 5'-linked ribonucleic acid that are 4 to 10 nucleotides in length, the by 2', 5' linked ribonucleotides are a 3', 5'-linked tetranucleotide (SEQ ID NO:1).

Wasner et al. teach a nucleic acid compound for inhibiting the RNAse H activity of a retroid virus reverse transcriptase comprising two complementary strands 18-23 nucleotides in length, wherein the strands can be RNA or DNA or both and further wherein the duplex comprise 3', 5'-linked or 2', 5'-linked RNA and comprise arabinonucleic acids (see Figure 1 and Table 1). Wasner et al. does not teach loop regions comprising SEQ ID NO. 1 nor does Wasner teach the self-complementary regions comprise an arabinonucleic acid.

Hannoush et al. teach a highly stabilizing tetranucleotide loop structure identical to SEQ ID NO. 1 that is incorporated into a 2', 5' linked ribonucleotides or a 3', 5'-linked

oligonucleotide compound (see Figure 1). Denisov et al. teach a hairpin duplex comprising an arabinonucleic acid that is a substrate for RNAse H (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate stabilizing tetranucleotide loops, as taught by Hannoush et al., and an arabinonucleic acid, as taught by Denisov et al. into the duplex taught by Wasner et al.

One would have been motivated to modify the oligonucleotide duplex taught by Wasner et al. with tetranucleotide loops identical to SEQ ID NO. 1 because Hannoush et al. teach hairpin structures comprising tetranucleotide loops are extremely stable and are important structural motifs for the design of synthetic ribozymes and aptamers (see page 12374, last paragraph). One would have been further motivated to incorporate an arabinonucleic acid into the hairpin duplex because Denisov et al. teach a hairpin duplex comprising an arabinonucleic acid increases the duplexes flexibility and binding affinity to the target and further can elicit RNase H activity. One would have been motivated to increase the stability and the binding affinity of the oligonucleotide duplex taught by Wasner et al. using tetranucleotide loops identical to SEQ ID NO. 1 because Wasner et al. teach the oligonucleotide duplexes are useful for targeting retroviral RNA to inhibit reverse transcription and more specifically, Wasner et al. teach *hairpin* aptamers are useful for inhibiting the removal of the RNA component of the RNA:DNA hybrid in retroviral RNA reverse transcription. Additionally, one would have been motivated to modify the oligonucleotide duplex taught by Wasner et al. because Hannoush et al. specifically teach the actual duplex taught in Wasner et al. is more stable when linked to the tetranucleotide loop having SEQ ID NO. 1 (see Abstract).

Finally, one would have a reasonable expectation of success because Wasner et al. teach a duplex for inhibiting of RNase H activity and teach inhibition of RNAse activity using said duplex (see Figure 7). Further, one would have a reasonable expectation of success because Hannoush et al. teach that an oligonucleotide duplex comprising a tetranucleotide loop, having the sequence identical to SEQ ID NO. 1, increased the duplex thermostability and further teach the actual hybrid duplex taught in Wasner et al. is more stable when linked to the said tetranucleotide loop (see Table 1and page 12374). Additionally, one would have a reasonable expectation of success because Denisov et al. teach increased flexibility and target specificity when a duplex comprises an arabinonucleic acid.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 and 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wasner et al. (Document AM on Form PTO-1449 filed 10/04/2004) in view of Hannoush et al. (Document AE on Form PTO-1449 filed 10/04/2004) and in further view of Ray et al. (FASEB J. 2000)

Claim 1 is drawn to a composition for inhibiting the RNase H activity of a retroid virus reverse transcriptase comprising an inhibitory agent comprising two complementary regions linked by 2', 5' ribonucleotides at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 wherein the complementary regions are between 2 and 24 nucleotides in length and comprise an arabinonucleic acid, 2'-fluoro-arabinonucleic acid, locked nucleic acid, peptide nucleic acid or a combination thereof and the complementary region is comprised of

deoxyribonucleic acid or ribonucleic acid. Claims 3-5 recite the complementary regions are comprised of 3-, 5'-linked ribonucleic acid, deoxyribonucleic acid or a combination of both. Claims 6-7 recites the complementary region comprises a 3-, 5'-linked ribonucleic acid that are 4 to 10 nucleotides in length, the by 2', 5' linked ribonucleotides are a 3', 5'-linked tetranucleotide (SEQ ID NO:1).

Wasner et al. teach a nucleic acid compound for inhibiting the RNAse H activity of a retroid virus reverse transcriptase comprising two complementary strands 18-23 nucleotides in length, wherein the strands can be RNA or DNA or both and further wherein the duplex comprise 3', 5'-linked or 2', 5'-linked RNA (see Figure 1 and Table 1). Wasner et al. does not teach loop regions comprising SEQ ID NO. 1 nor does not teach either strand of the antiparallel complementary oligonucleotide comprises a peptide nucleic acid.

Hannoush et al. teach a highly stabilizing tetranucleotide loop structure identical to SEQ ID NO. 1 that is incorporated into a 2', 5' linked ribonucleotides or a 3', 5'-linked oligonucleotide compound (see Figure 1). Ray et al. teach incorporation of a peptide nucleic acid into a duplex increases the duplex stability and sequence specificity of the duplex (see abstract page 1041).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the complementary regions of the duplex taught by Wasner et al. with a peptide nucleic acid as taught by Ray et al.

One would have been motivated to modify the oligonucleotide duplex taught by Wasner et al. with tetranucleotide loops identical to SEQ ID NO. 1 and a peptide nucleic acid because Hannoush et al. teach hairpin structures comprising tetranucleotide loops are extremely stable

and are important structural motifs for the design of synthetic ribozymes and aptamers (see page 12374, last paragraph) and Ray et al. teach peptide nucleic acids are synthetic molecules that can bind with high sequence specificity to a chosen target in a gene sequence and further Ray et al. teach that hybrid complexes containing a peptide nucleic acid exhibit extreme thermal stability and unique ionic strength (see Abstract and page 1043 column 2). Additionally, one would have been motivated to modify the oligonucleotide duplex with a peptide nucleic acid because Ray et al. teach peptide nucleic acids have very specific interactions with DNA and RNA making them very promising in therapeutic and diagnostic applications (see page 1057). Further, one would have been motivated to increase the stability and target specificity of the oligonucleotide duplex taught by Wasner et al. with tetranucleotide loops identical to SEQ ID NO. 1 because Wasner et al. teach the oligonucleotide duplexes are useful for targeting retroviral RNA to inhibit reverse transcription and more specifically, Wasner et al. teach *hairpin* aptamers are useful for inhibiting the removal of the RNA component of the RNA:DNA hybrid in retroviral RNA reverse transcription.

Finally, one would have a reasonable expectation of success because Wasner et al. and Hannoush et al. teach inhibition of RNAse activity using said duplex (see Figure 7) and because Ray et al. teach targeting a gene sequence using a duplex comprising a peptide nucleic acid and further teach inhibition of gene activity using a duplex comprising a peptide nucleic acid (see page 1047-1048). Additionally, one would have a reasonable expectation of success because Hannoush et al. teach that an oligonucleotide duplex comprising a tetranucleotide loop having the sequence identical to SEQ ID NO. 1 increase the duplex thermostability and further teach the

actual hybrid duplex taught in Wasner et al. is more stable when linked to the said tetranucleotide loop (see Table 1and page 12374).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Claim Rejections - 35 USC § 112

The rejection of record of claims 1-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in response to Applicant's amendments filed 10/21/2005.

Claim Rejections - 35 USC § 102 or 35 USC § 103

The rejection of record of claims 1-7 under 35 U.S.C. 102(b) or 35 U.S.C. 103(a) as being anticipated by or obvious over Hannoush et al. (Document AE on Form PTO-1449 filed 10/04/2004) is withdrawn in response to Applicant's amendments filed 10/21/2005.

The rejection of record of claims 1-5 under 35 U.S.C. 102(b) or 35 U.S.C. 103(a) as being anticipated by or obvious over Wasner et al. (Document AM on Form PTO-1449 filed 10/04/2004) is withdrawn in response to Applicant's amendments filed 10/21/2005.

The rejection of record of claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Andreola et al. (Document AA on Form PTO-1449 filed 10/04/2004), in view of Park et al. (Document AJ on Form PTO-1449 filed 10/04/2004) and in further view of Hannoush et al.

(Document AE on Form PTO-1449 filed 10/04/2004) is withdrawn in response to Applicant's arguments filed 10/21/2005.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of

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Kimberly Chong
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